PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/US2004/041331	International filing date *(day/month/year)* 09.12.2004	Priority date *(day/month/year)* 09.12.2003
International Patent Classification (IPC) or national classification and IPC A61K9/16, A61K9/20		
Applicant UNIVERSITY OF NORTH TEXAS et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.10.2005	17.03.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Felder, C Telephone No. +49 89 2399-7852

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/041331

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-35 as originally filed

Claims, Numbers

1-47 filed with telefax on 03.10.2005

Drawings, Sheets

1-29 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-47
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-47
Industrial applicability (IA)	Yes:	Claims	1-47
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V.

1 Reference is made to the following documents:

D1 : DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 8 August 2001 (2001-08-08), GAN D ET AL: "Tunable swelling kinetics in core--shell hydrogel nanoparticles." XP002330084 Database accession no. NLM11480971

D2 : BOYKO V ET AL: "Thermo-sensitive poly(N-vinylcaprolactam-co-acetoacetoxyeth yl methacrylate) microgels: 1-synthesis and characterization" POLYMER, ELSEVIER SCIENCE PUBLISHERS B.V, GB, vol. 44, no. 26, December 2003 (2003-12), pages 7821-7827, XP004475138 ISSN: 0032-3861

D3 : US 4 575 539 A (DECROSTA ET AL) 11 March 1986 (1986-03-11)

D4 : DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 2000, SENFF H ET AL: "Influence of cross-link density on rheological properties of temperature-sensitive microgel suspensions" XP002330085 Database accession no. EMB-2000328241

D5 : DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; July 2002 (2002-07), VIHOLA HENNA ET AL: "Binding and release of drugs into and from thermosensitive poly(N-vinylcaprolactam) nanoparticles" XP002330086 Database accession no. PREV200200450428

The present application describes an aqueous dispersion of hydrogel nanoparticles comprising interpenetrating polymer network (IPN) nanoparticles and the preparation thereof.

1. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-47 is not new in the sense of Article 33(2) PCT.

The documents **D1-D5** discloses all an aqueous dispersion of hydrogel nanoparticles comprising interpenetrating polymer network (IPN) nanoparticles.

Document **D3** discloses interpenetrating polymer network nanoparticles with two polymer networks and substantially free of a shell and core polymer configuration. Documents **D1, D2, D4 and D5** all discloses interpenetrating polymer network nanoparticles with either one or even two polymer networks. All of said interpenetrating polymer network nanoparticles are thermosensitive and thermoreversible gelation will occur, since they are of the same or at least a similar composition as in the present application.

The product claimed in claims 1-14 and 41-47 is not novel over the prior art *per se*. A new process of preparation does not necessarily lead to a new product. A new product must have structural differences to the product in the prior art. If applicant questions novelty of said product, said differences must be demonstrated.

2. Inventive step

Should the applicant overcome the abovementioned novelty objections, he should turn his attention to the relevance of **D1-D5** with regard to the inventive step of the claimed subject-matter.
Starting from document **D3** a person skilled in the art confronted with the problem to created an interpenetrating polymer network nanoparticles with two polymer networks, free of a core and shell polymer configuration and thermoreversible behaviour would find enough hints in any of documents **D1, D2, D4 or D5** to get a solution as proposed in the present application.
Even if it is not explicitly mentioned that the gelation is thermoreversible, it is obvious that if the composition is the same, the behaviour will be the same, at least as long as no other evidence nor proof is shown.

3. Industrial applicability

The present claims 1-47 seem to be industrially applicable.

WHAT IS CLAIMED IS:

1. An aqueous dispersion of hydrogel nanoparticles, comprising:
interpenetrating polymer network ("IPN") nanoparticles, wherein each IPN nanoparticle comprises a first polymer network interpenetrating a second polymer network; and
an aqueous medium;
wherein, the IPN nanoparticles are substantially free of a shell and core polymer configuration; and the aqueous dispersion of hydrogel nanoparticles can undergo a reversible gelation in response to a change in stimulus applied thereon.

2. The aqueous dispersion of hydrogel nanoparticles of claim 1, further comprising a biologically active material.

3. The aqueous dispersion of hydrogel nanoparticles of claim 2 wherein the biologically active material is: a drug, a pro-drug, a protein, or a nucleic acid.

4. The aqueous dispersion of hydrogel nanoparticles of claim 1, wherein the stimulus comprises a change in temperature.

5. The aqueous dispersion of hydrogel nanoparticles of claim 4, wherein the temperature change above a gelation temperature ("Tg") induces a volume phase transition of the IPN nanoparticles, resulting in an inverse thermo-thickening property of the aqueous dispersion of hydrogel nanoparticles.

6. The aqueous dispersion of hydrogel nanoparticles of claim 5, wherein the inverse thermo-thickening property is a transformation from a low-viscous fluid to a gel when heated above the Tg.

7. The aqueous dispersion of hydrogel nanoparticles of claim 5, wherein the Tg is about 34°C.

8. The aqueous dispersion of hydrogel nanoparticles of claim 1, wherein the first polymer network comprises poly(N-isopropylacrylamide) or hydroxypropylcellulose.

9. The aqueous dispersion of hydrogel nanoparticles of claim 1, wherein the second polymer network comprises poly(acrylic acid).

10. The aqueous dispersion of hydrogel nanoparticles of claim 1, wherein the first polymer network comprises poly(N-isopropylacrylamide) and the second polymer network comprises poly(acrylic acid).

11. The aqueous dispersion of hydrogel nanoparticles of claim 1, wherein the mono-disperse nanoparticles have a uniformed sized hydrodynamic radius.

12. The aqueous dispersion of hydrogel nanoparticles of claim 1, wherein the mono-disperse nanoparticles have an average hydrodynamic radius in the range from about 75 nm to about 200 nm.

13. The aqueous dispersion of hydrogel nanoparticles of claim 1, wherein the first polymer network and second polymer network in the mono-disperse nanoparticles have weight ratio of about 1:1.88.

14. The aqueous dispersion of hydrogel nanoparticles of claim 1, wherein the first polymer network and the second polymer network form a total polymer having a concentration range from about 1.25 wt% to about 5.25 wt% in distilled water.

15. A method of preparing an interpenetrating polymer network ("IPN") of mono-disperse nanoparticles, comprising:

(a) providing a first mono-dispersed polymer nanoparticle prepared by mixing a first monomer, a surfactant, a first cross linking agent, and a first initiator at a first temperature;

(b) adding to the first mono-dispersed polymer nanoparticle a second monomer, a second cross linking agent, a second initiator and an activator forming a nanoparticle solution;

(c) mixing the nanoparticle solution for a period of time at a second temperature to form the IPN of mono-disperse nanoparticles; and

(d) isolating the IPN of mono-dispersed nanoparticles;

wherein the first monomer, the first cross linking agent, the second monomer, and the second cross linking agent are substantially free from dissolved oxygen gas.

16. The method of claim 15, further comprising (e) mixing the isolated IPN of mono-dispersed nanoparticles with a biologically active material at a third temperature.

17. The method of claim 16, wherein the biologically active material is a drug, a pro-drug, a protein, or a nucleic acid.

18. The method of claim 16, wherein the third temperature is below a gelation temperature ("Tg") of the IPN of mono-disperse nanoparticles in an aqueous mixture.

19. The method of claim 18, wherein the Tg is about 33°C.

20. The method of claim 15, wherein the first mono-disperse polymer comprises poly(N-isopropylacrylamide) or hydroxypropylcellulose.

21. The method of claim 15, wherein the second monomer comprises poly(acrylic acid).

22. The method of claim 15, wherein the first mono-dispersed polymer nanoparticle comprises poly(N-isopropylacrylamide) and the second monomer comprises acrylic acid.

23. The method of claim 15, wherein the first cross linking agent comprises N,N'-methylenebisacrylamide; the second cross linking agent comprises N,N'-methylenebisacrylamide; the first initiator comprises potassium persulfate; the second initiator comprises ammonium persulfate; the surfactant comprises sodium dodecyl sulfate ("SDS") and the activator comprises TEMED.

24. The method of claim 15, wherein the IPN of mono-dispersed nanoparticles have an average hydrodynamic radius in the range from about 75 nm to about 200 nm.

25. The method of claim 15, wherein the period of time is less than 130 minutes.

26. The method of claim 25, wherein the period of time about 120 minutes.

27. The method of claim 15, wherein the first temperature is about 70°C.

28. The method of claim 15, wherein the second temperature is about 21°C.

29. A method of preparing a nanocluster of cross-linked interpenetrating polymer networks ("IPN") nanoparticles, comprising:

(a) providing a dispersion of IPN nanoparticles;

(b) adding a first cross linking agent and a second cross linking agent to the dispersion of IPN nanoparticles, forming an IPN cross linking solution; and

(c) heating the IPN cross linking solution to a first temperature for a period of time forming the nanocluster of cross-linked IPN nanoparticles;

wherein, the mono-dispersed IPN nanoparticles have a uniformed size and comprise a first polymer network interpenetrating a second polymer network and is substantially free from a shell and core polymer configuration; the mono-dispersed IPN nanoparticles can undergo a reversible gelationin response to a change in stimulus applied thereon.

30. The method of claim 29, further comprising (d) mixing the nanocluster of cross-linked IPN's with a biologically active material at a second temperature.

31. The method of claim 30, wherein the biologically active material is a drug, a pro-drug, a protein, or a nucleic acid.

32. The method of claim 30, wherein the second temperature is below a gelation temperature ("Tg") of the nanocluster of cross-linked IPN nanoparticles in an aqueous dispersion.

33. The method of claim 32, wherein the Tg is about 33°C.

34. The method of claim 29, wherein the first polymer network comprises poly(N-isopropylacrylamide) and the second polymer network comprises poly(acrylic acid).

35. The method of claim 29, wherein the first cross linking agent comprises 1-ethyl-3(3-dimethylaminopropyl) carbodiimide hydrochloride ("EDAC"); and the second cross linking agent comprises adipic acid dihydrazide.

36. The method of claim 29, wherein the nanocluster of cross-linked IPN's an average hydrodynamic radius in the range from about 155 nm to about 250 nm.

37. The method of claim 36, wherein the nanocluster of cross-linked IPN's have an average hydrodynamic radius in the range from about 225 nm to about 240 nm.

38. The method of claim 29, wherein the period of time is about 25 to about 45 minutes.

39. The method of claim 38, wherein the period of time is about 33 to about 37 minutes.

40. The method of claim 29, wherein the first temperature is about 44°C.

41. A nanocluster of cross-linked interpenetrating polymer network ("IPN") nanoparticles, comprising: at least two IPN nanoparticles linked by a cross-linking group; wherein, the each IPN nanoparticle have a uniformed size and comprise a first polymer network interpenetrating a second polymer network and is substantially free from a shell and core polymer configuration.

42. The nanocluster of claim 41, further comprising a biologically active material.

43. The nanocluster of claim 42, wherein the biologically active material is a drug, a pro-drug, a protein, or a nucleic acid.

44. The nanocluster of claim 41, wherein the first polymer network comprises poly(N-isopropylacrylamide) and the second polymer network comprises poly(acrylic acid).

45. The nanocluster of claim 41, wherein the cross linking group comprises adipic acid dihydrazide.

46. The nanocluster of claim 41, wherein the uniformed sized nanoparticles have an average hydrodynamic radius in the range from about 155 nm to about 250 nm.

47. The nanocluster of claim 46, wherein the nanoparticles have an average hydrodynamic radius in the range from about 180 nm to about 1000 nm.